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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/802,518	03/09/2001	Gary Van Nest	377882001100	9215

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/802,518	VAN NEST, GARY	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-16,18-25,27,28,33 and 36-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-16,18-25,27,28,33 and 36-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 20 October 2003 has been entered. This Office Action is a reply to the Request for Continued Examination and "Amendment and Response under 37 CFR §1.114" of 20 October 2003 (hereinafter, 20 October Paper) filed in response to the Final Office Action mailed 17 June 2003 (hereinafter, 17 June Office Action). Claims 1-6, 8-16, 18-25, 27, 28 and 33 were considered in the 17 June Office Action. Claims 1, 10 and 20 were amended and claims 36-39 were added in the 20 October Paper. Claims 1-6, 8-16, 18-25, 27, 28, 33 and 36-39 are presently pending and under consideration.

Response to Amendment

Claims 1-6, 8-16, 18-25, 27, 28 and 33 stand rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claimed subject matter for reasons of record and herein below in the "Response to Arguments".

New grounds for rejection are set forth herein below.

Response to Arguments

Claims 1-6, 8-16, 18-25, 27, 28 and 33 were rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for a method of reducing the severity of a symptom of herpes virus infection in any individual or mammal comprising administering any sequence comprising 5'-C,G-3' sequence. It was indicated that the specification is enabling only for a method of preventing symptoms of, reducing severity of or reducing recurrence of a symptom of herpes infection in mice and guinea pigs challenged with herpes virus, by administering the *phosphorothioate* polynucleotide comprising the immunostimulatory sequences set forth as SEQ ID NO:1 and 9 to said mice and guinea pigs at a dose sufficient to prevent, or reduce severity or recurrence of a symptom of herpes infection.

As will be discussed in detail herein below, the disclosure is also enabling for a method of reducing the severity or recurrence of a symptom of herpes simplex virus infection in a human infected with herpes simplex virus comprising administering an ISS comprising SEQ ID NO:1.

In response to the arguments of record, Applicant contends that the specification provides sufficient guidance to enable the skilled artisan to make and use the full scope of the claimed invention. Applicant points to examples of methods for synthesis, formulation and administration of ISS-containing polynucleotides as well as means of assessing the functional activity of the ISS-containing polynucleotides. However, all of the teachings cited are general in nature and do not address the unpredictable nature of ISS effect. As established in previous Office Actions, the effect of any given ISS on one mammalian species cannot be predicted based on the response obtained in another mammalian species, even if the two species are closely related. Thus, with regard to species other than mouse or guinea pig or ISS other than those demonstrated to be effective, the teachings provide no more than a plan for empirical experimentation wherein each

of the ISS in the enormous genus contemplated are tested in each species of the genus mammalia. The claims are not limited to any particular dosage or mode of administration, and the ISS administered can be any nucleic acid under 200 nucleotides in length comprising the dinucleotide 5'-C,G-3'. Given the unpredictability of the art, it is more likely than not that the vast majority of ISS encompassed by the claim would not work in the vast majority of species of mammal encompassed by the claim (i.e., inoperative embodiments). It would therefore require undue experimentation to identify the operative embodiments of the claimed invention.

Next, Applicant argues that polynucleotides with immunostimulatory sequences active in cells of many mammalian species have been described in scientific literature. This argument is not deemed persuasive because the rejected claims are not limited to any particular species of mammal and, as discussed in previous Office Actions, the relevant art does not enable the skilled artisan to readily extend findings obtained with one species of mammal to another species of mammal.

Applicant urges that the test for enablement is not whether a certain amount of experimentation is required to practice the invention, but rather whether the amount of experimentation is "undue". This argument has been addressed in previous Office Actions. To summarize, the argument fails to take into account the breadth of the claims and the unpredictability of extending the teachings of the specification to all mammalian species. In *In re Wands*, the court states, "[t]he determination of what constitutes undue experimentation in a given case requires the application of standard reasonableness, having due regard for the nature of the invention and the state of the art" (at 1404). The class Mammalia includes approximately 5,000 species, and, as described above, even closely related species differ dramatically in their response to any given

CpG-containing oligonucleotide. Although the relative level of skill in the art is high, the art is immature and the factors dictating efficacy of CpG-containing oligonucleotides in mammals are largely unknown. Therefore, in order to practice the claimed invention according to its full scope, the skilled artisan would have to identify, by blind trial and error experimentation, an immunostimulatory oligonucleotide capable of eliciting an immune response of sufficient magnitude to prevent a symptom of herpes virus infection in each of the approximately 5,000 species encompassed by the claim. Clearly, the amount of experimentation required is beyond what would be considered reasonable or routine in the art.

Finally, Applicant cites several issued patents which contain claims wherein the scope of the claims and disclosure alleged to be similar to the instant case. First, it should be made clear that each patent application must be examined on its own merits and the allowance of similar claims to others is immaterial to the allowability of the instant claims (see *In re Giolito*, 530 F.2d 397, 188 U.S.P.Q. 645 (C.C.P.A. 1976). Furthermore, the patented claims are significantly different from the instant claims and from each other (i.e., directed to treatment of different conditions or to providing different outcomes using different treatment regimens). Thus, the cited patents cannot be taken as evidence for any particular Office policy on ISS treatment.

Applicant's arguments have been fully considered but are not deemed persuasive individually or as a whole. Therefore, the claims stand rejected as lacking enablement for the full scope of the claimed subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing the severity or recurrence of a symptom of herpes simplex virus in a human comprising administering a composition comprising an ISS comprising SEQ ID NO: 1, wherein the polynucleotide comprises a phosphate backbone modification, does not reasonably provide enablement for a method of preventing a symptom of herpes simplex virus infection in a human or a method of reducing the severity or recurrence of a symptom of herpes simplex virus in a human comprising administering a composition comprising any ISS. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claims are directed to methods of preventing or reducing the severity or recurrence of a symptom of herpes virus infection in a human comprising administering an ISS. As the claims are not limited to any particular ISS, the

claims broadly encompass treating a human with any nucleic acid comprising the dinucleotide 5'-C,G-3'.

With regard to preventing a symptom of herpes virus infection, the specification teaches that the symptom does not appear. Thus, the specification must teach the skilled artisan how to treat a human who has been exposed to herpes simplex virus such that a symptom of herpes simplex virus infection does not appear.

State of the prior art and level of predictability in the art: The state of the art with regard to predictability of immunostimulatory responses elicited by CpG-containing nucleic acids is established in previous Office Actions. To review, use of CpG sequences as an immunostimulatory adjuvant is well know in the art. However, according to the teachings of Agarwal and Kandimalla (cited as Ref. No. 13 in Paper No. 11), published well after the effective filing date of the instant application, "Although the presence of an unmethylated CpG dinucleotide is essential for the induction of an immunostimulatory activity, the sequences flanking the CpG dinucleotide also play a role", human immune cells respond poorly to the hexameric motif found to be optimal in activating the mouse immune system "suggesting that the sequences required for CpG-related immune stimulation varies from species to species" and "the optimal CpG sequence requirement for many other animal species is not known" (beginning page 114, column 2 final paragraph and continued through the first paragraph of page 115). Furthermore, Agarwal and Kandimalla (*supra*) teach, "Studies on the medicinal chemistry of CpG DNA have just begun..." and "There is a species-dependent selectivity of CpG DNA, and the optimal CpG DNA sequences for many vertebrate species are not known yet. Medicinal chemistry could help to resolve the issues of species-selective bias of CpG DNA motifs and

permit the application of CpG DNA therapeutics for treating veterinary diseases without requiring the identification of optimal sequences for each species" (page 119, column 2, first and second paragraphs of the Concluding Remarks). These comments demonstrate the high degree of uncertainty in the art with regard to extending results obtained using ISS DNAs in one species to other species of mammals and in establishing which CpG-containing sequences will be effective in a given species. In particular, Hartmann *et al.* (2000) *J. Immunol.* 164:1617-1624 (previously made of record) teach that findings obtained using ISS in mice could not be extended to humans. Hartmann *et al.* teach, "[r]ecently, we found that phosphorothioate ODN with the purine-purine-CG-pyrimidine-pyrimidine formula that had been identified as the most stimulatory motif in mice show no or only weak activity in human immune cells" (final paragraph on page 1617) and conversely, "[t]he human stimulatory ODN…shows weaker activity in mice compared with the highly active murine CpG ODN…supporting the concept of species specificity of CpG DNA recognition by immune cells" (second paragraph on page 1622). Hartmann *et al.* also teach that the effectiveness of any given ISS is unpredictable even within closely related mammalian species. In the second paragraph on page 1622, Hartmann *et al.* teach, "[a]lthough ODN 2006 was active in vitro in all primates tested, other CpG ODN, such as ODN 2007, had relatively high activity in human immune cells but no or a weaker effect in chimpanzees and rhesus monkeys." These teachings demonstrate the unpredictability of obtaining a useful response to any given CpG-containing oligonucleotide in any given species. Thus, without specific guidance, the skilled artisan is unable to extend findings obtained using ISS DNAs in one species to other species of mammals or to establish which CpG-containing sequences will be effective in a given species without having to engage in empirical experimentation.

The art does teach that the nucleic acid set forth as SEQ ID NO: 1, which is demonstrated in the instant specification to be effective in animal models of herpes virus infection, is capable of eliciting an effective immune response in humans (see Pyles *et al.* (2002) *J. Virol.* 76:11387-11396, first paragraph on page 11388 and references cited therein). Thus, the skilled artisan would expect that the findings obtained using the sequence set forth as SEQ ID NO: 1 could, more likely than not, be extended to human.

Amount of direction provided by the inventor and existence of working examples: The instant disclosure provides various nucleic acid sequences comprising 5'-CpG-3' and reduction to practice of phosphorothioate oligonucleotides comprising two of those sequences for the treatment of herpes virus infection in mice and guinea pigs. The disclosure does not, however, set forth teachings regarding the requirements for an immunostimulatory oligonucleotide effective in humans beyond the sequence set forth as SEQ ID NO:1.

With regard to preventing a symptom of herpes simplex virus infection, the specification teaches that the incidence of symptoms in mice treated at 2 hours and 6 hours after inoculation was 60% and 80%, respectively, as opposed to 100% in untreated animals (see especially Table 1). Example 3 of the specification teaches that recurrence of disease in guinea pigs was not prevented by ISS treatment. Given these data, the skilled artisan would perceive that, to be effective in preventing a symptom the immunostimulatory sequence would have to be administered within a narrow window of time after infection.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not be able to practice the full scope of the claimed invention without having to engage in undue

experimentation. The teachings of the specification demonstrate that a single oligonucleotide known to be effective in humans is capable of reducing the severity or recurrence of a symptom of herpes simplex virus in animal models. However, the art teaches that the sequence requirements for effective immunostimulation in any given species of mammal are unpredictable. Thus, the skilled artisan is unable to readily identify other immunostimulatory sequences that would be effective in the claimed method and would have to engage in undue trial and error experimentation to identify other oligonucleotide sequences that could be used in the method.

With regard to preventing a symptom of herpes simplex virus infection in a human. The teachings of the specification suggest that effective prevention requires that the immunostimulatory oligonucleotide be administered within a limited window. As the claims are not limited to administering the oligonucleotide at any particular time after infection and it appears that administration at most time points after infection would be ineffective, the skilled artisan would have to experiment unduly to establish which treatment regimens falling within the scope of the claim would be effective in preventing a symptom of herpes simplex virus infection.

Thus, due to the art recognized unpredictability of therapeutic application of immunostimulatory sequences and the lack of guidance in the specification or prior art with regard to effective immunostimulatory sequences in humans and effective treatment regimens for preventing a symptom of herpes simplex virus infection in humans, it would require undue experimentation to practice the invention commensurate with the full scope of the claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Please note: Art Unit 1636 will be moving to the new USPTO facilities on 14 January 2004. After that date, Examiner Sullivan can be reached at 571-272-0779 and Examiner Yucel can be reached at 571-272-0781.

DMS

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER